III. REMARKS

Claim Status

Claims 1-2, 4, 8 and 10-11 are currently under examination on the merits. Claims 28-31 are newly presented.

Claim Rejections - 35 USC § 103(a)

Claims 1-2, 4, 8 and 10-11 stand rejected under 35 U.S.C. 103(a) as being obvious over by McSwiggen et al. (US 60/396,600) hereafter McSwiggen II) (US 2005/0153916 A1) in view of Vickers et al. (*The Journal of Biological Chemistry*, 2003, 278:7108-7118).

Applicant traverses this ground for rejection.

As stated by the examiner, in Table II at page 85 of McSwiggen II there are disclosed various target sites for human telemorase RNA sequence including antisense polynucleotide sequences within the region of 2206-2225 and 2331-2350.

The examiner concludes that since the antisense oligonucleotide sequences complementary to the claimed target sequence region were contemplated by McSwiggen II prior to the earliest filing date granted in the instant application, the claimed invention taken as a whole would have been *prima facie* obvious at the time of the invention.

Applicant respectfully traverses this ground for rejection.

As to the identity of the sequences disclosed by McSwiggen et al., (US 2005/0153916 A1) (hereafter McSwiggin I) in the previous office action, the examiner identified SEQ ID NO: 530

of McSwiggen I as disclosing a target for a sense siNA molecule as being a 22 nucleotide sequence which encompassed the 20 nucleotide target for applicant's antisense molecule.

As recognized by the examiner, applicant's priority date pre-dates the McSwiggen I publication. Thus, the examiner in the current rejection relies on McSwiggen II, a provisional application dated July 2, 2002, which pre-dates applicants application.

The examiner cites page 85 of McSwiggen II as disclosing antisense polynucleotide sequences within applicant's claimed regions of 2206-2225 and 2331-2350. However, none of the cited sequences of McSwiggen are commensurate with the two claimed sequence regions of the present invention.

And at no point does McSwiggen II disclose an unmodified antisense sequence which is equivalent to a cited target region.

With regard to applicant's target 2206-2225, McSwiggen II discloses targets 2199-2220, 2197-2219, and 2201-2221. Thus although McSwiggen II is very careful, in a 7 page listing of 100's of sequences, to list target sequences surrounding the sequence claimed by applicant and encompassed by the later disclosure of McSwiggen I, the provisional application does not disclose the target identified by applicant as having specific functionality.

With regard to applicant's target 2331-2350, McSwiggen II discloses targets 2325-2346, 2345-2365, 2341-2363, and 2343-2363. Thus although McSwiggen II is very careful, in a 7 page listing of 100's of sequences, to list target sequences surrounding the sequence claimed by applicant and encompassed by the later disclosure of McSwiggen I, the provisional application does not disclose the target identified by applicant as having

specific functionality.

McSwiggen II's listing of 100's of sequences is so specific that on the principle of *expressio unius est exclusio alterius* his inclusion of so many varieties would clearly lead one skilled in the art away from expecting others to be functional.

As disclosed in McSwiggen II, the subject-matter of the application is siRNA molecules which are stated to be are able to treat a variety of pathology indications. McSwiggen II specifically defines siRNA as a double stranded nucleic acid molecule capable of RNA interference (page 33).

Further, McSwiggen II's antisense sequences show "at least one chemically modified nucleotide or non-nucleotide at the 3' end of the antisense strand". The authors argue, on page 49, line 24-26, that nucleic acids having chemical modifications that maintain or enhance activity are provided and that these are more resistant to nucleases than unmodified nucleic acids.

Contrary to McSwiggen II, applicants selected two defined target regions (regions 2206-2225 and 2331-2350) and surprisingly discovered that the direct complementary antisense oliqos (ASt2206 and ASt 2331) provide significant benefits not obtained from other sequences.

As set forth in applicants' specification, these two oligos - sequences No. 10 and 13 (ASt2206 and ASt 2331) - cause a reduction in viability of EJ 28 cells of more than 65% compared to other oligos and the nonsense control (Example 1 and Fig. 2).

Furthermore these oligos cause a synergistic booster effect if simultaneously administered with chemotherapeutics (cf. Example 2, Fig. 5).

The beneficial effect of these specific molecules is set forth in the paper manuscript authored by the inventors supplied herewith.

As stated at column 2 on page 1 of the manuscript, the aim of the presented study was to characterize genome-wider expression profiles of the BCa cell line EJ28 after transfection with 2 hTERT ASODNs [namely with the selected oliqos ASt2206 (SEQ ID NO. 10) and ASt2331 (SEQ ID NO. 13)] as the molecular basis of their growth suppressing function.

After multiple cycles of an instillation therapy (based on an anti-hTERT-AS-ODN transfection followed by chemotherapy at the next day, two times per week, time period of 2 to 3 weeks) against orthotopically superficial human bladder cancer cells (cell line EJ28), a significantly reduced tumor growth compared to the control treatment (only chemotherapy) was found in a mouse model. Dramatically smaller tumor volumes or an absence of tumor formation were determined for several mice of the combinational treatment group (AS-ODN + chemotherapy). Surprisingly, a relatively large amount of the tumor tissue was not viable (netrotic areas) in those treated animals with detectable tumor masses. These inhibition effects were exclusively observed for the treatment group consisting of anti-hTERT AS-ODN. Moreover, detailed histological examinations indicated a massive induction of apoptosis as well as significant locally inflammation. The exact mechanisms of this therapeutic efficacy is unknown so far for the in vivo model, however, the observed enhancing effect of the AS-ODN-therapy is a significant feature of the AS-ODN constructs. This implies a heterogeneous, complex and significantly anti-proliferate efficiency of these molecules against human bladder tumors.

As stated at column 1 on page 3 (F3 paragraph), the 2 hTERT AS-ODNs caused total numbers of changed genes of 59 (ASte12206) and

101 (AStel2331), respectively, whereby most of them were upregulated (Fig. 3a).

Referring to column 2 of page 3 (F4 paragraph), the inventive 2 hTERT AS-ODNs efficiently reduced the numbers of EJ28 cells within the first 24 hr after transfection in comparison to the NS-ODN (Fig, 4).

In addition to the showing of the particular surprising effectiveness of the selected regions, the choice of these two specific target regions to obtain these significant benefits was not obvious to a person skilled in the art. As recognized by the Court in In re Carleton (CCPA 1997) 599 F2d 1021, 202 USPQ 165, chemistry is a largely empirical science and therefore there is often great difficulty in predicting how to given compound will behave.

Furthermore, where the prior art gives no indication of which parameters are critical and no direction as to which of many possible choices is likely to be successful, the fact that the claimed combination falls within the scope of possible combinations taught therein does not render it unpatentably obvious. In re O'Farrell (CAFC 1988) 853 F2d 894, 7 PQ2d 1673; Ex parte Obukowicz (BPAI 1992) 27 PQ 1063; Ex parte Strobel (BOPA 1968) 160 USPQ 352. This is especially true where hundreds of possible selections from the prior art are possible and where the art does not encompass the claimed oligo in its entirety.

Vickers et al. is cited as demonstrating that “siRNA molecules and antisense oligonucleotides are functionally equivalent…”

Applicant respectfully disagrees that Vickers et al. teaches the functional equivalence of the two types of molecules.

At page 7117 Vickers et al. states that although the two types

of antisense oligonucleotides behave similarly in terms of potency, maximal effects, specificity and duration of action and efficiency, “[i]t remains to be determined whether siRNA molecules work broadly for in vivo applications.” Thus, at best, Vickers et al. is an invitation to do further testing to determine whether these molecules are in fact equivalent in effect.

Even assuming, *arguendo,* that one skilled in the art would consider it "obvious to try" what the inventor did, that does not create *prima facie* obviousness. There is usually an element of "obvious to try" in any research endeavor, since such research is not undertaken with complete blindness but with some semblance of a chance of success.

For all the above reasons, applicant requests favorable reconsideration of the rejection and early allowance of the claims. The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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